

REMARKS

The Applicants hereby gratefully acknowledge the withdrawal of the objections and rejections made in the Office Action of February 11, 2008. Remaining for consideration are rejections made pursuant to 35 USC 102(b) and 35 USC 103(a).

Claims 1-6 and 8-19 are pending. No substantive issues are raised with respect to the minor amendments made herein to claims 1 and 16. These amendments correct a typographical error in the recitation of w/v% instead of w/w%; see page 7, lines 17-20 in the specification.

Claims 1-6, 8, 10-13, 16 and 17 have been rejected under 35 USC 102(b) as being anticipated by Harada et al. Claims 1, 9 and 14-19 have been rejected under 35 USC 103(a) as being unpatentable over Harada et al in view of Wall (USP 5,340,817). These rejections are hereby respectfully traversed. Reconsideration and withdrawal thereof are requested.

1) Novelty of the present invention

In Harada et al., as indicated by the Examiner, there are disclosed (a) a camptothecin derivative (T-0128) prepared by binding a camptothecin compound (T-2513) with carboxymethylated dextran via gly-gly-glycine, (b) an aqueous solution of 100 μ g/mL of T-0128 (5 μ g/mL as T-2513: "A solution" hereinafter) and (c) a solution of T-0128 in saline (0.5mg/mL as T-2513) ("B solution" hereinafter)). However, the concentration of T-0128 in the above "A solution" is 0.1mg/mL (0.01w/v%), and this solution is, in this respect, clearly different from the present invention. Furthermore, the concentration of T-0128 in the above "B solution" is 100mg/mL (10w/v%; according to Harada et al., 5 μ g of T-2513 corresponds to 100 μ g of T-0128), but the solution of Harada is a

solution in saline without any buffer and therefore, in this respect, is also clearly different from the present invention. Since anticipation requires that each and every one of the claim limitations must be disclosed in a single reference, the novelty of the present invention under 35 USC 102(b) is not applicable and the rejection based thereon should be withdrawn.

2) Unobviousness of the present invention

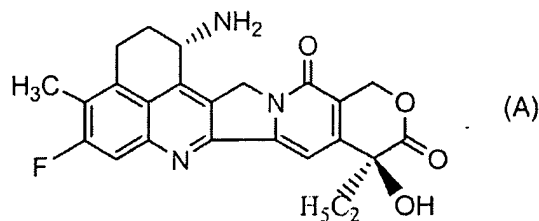
Harada et al. disclose the same compound (T-0128) as the camptothecin derivative in the present invention, and an aqueous solution consisting of specific ingredients including said compound. However, in Harada et al., there is neither a description nor a suggestion on preservative stability in the preparation containing a camptothecin derivative whether or not it is in a liquid form or a lyophilized form.

Furthermore, the Examiner indicates that in Wall et al., an aqueous solution containing the above-mentioned camptothecin analog and a lyophilized product containing a specific camptotecin analog (in Examples 18 and 19) are described. However, the camptothecin analog described in Wall is not a compound containing a polysaccharide such as dextran, etc. as its constituent-component. On the other hand, the camptothecin derivative of the present invention and disclosed in Harada et al., is a macromolecule containing carboxymethylated polysaccharide as its constituent-component, and the derivative in the present invention is structurally completely different from the camptothecin analog described in Wall et al. Further, the lyophilized product in Example 18 or 19 of Wall et al. is a camptothecin analog in the state of a solid and is essentially different from the preparation of the present invention, which is prepared by lyophilizing an aqueous solution containing the camptothecin derivative adjusted to pH 5 to 8 with a buffer. As such, Wall et al. disclose a compound which is completely structurally different from the compound in the present invention and its lyophilized preparation. Therefore,

it is submitted that it would be difficult for the skilled person in the art to find a reason to combine Harada et al. and Wall et al. in relation to the present invention, since Wall et al. only disclose a compound that is structurally different from the compound of the present invention and its lyophilized product. Furthermore, the Examiner's consideration that one would be motivated to combine Harada et al. and Wall et al. cannot be rationalized as discussed below.

For drugs that are unstable in an aqueous solution, lyophilization is generally used for stabilization. However, regarding a DDS-camptothecin as claimed in the present application, it had been considered before the filing of the present application that stabilization by lyophilization of this compound is not suitable. For example, in WO02/05855 which was published before the priority date of the present application, there is disclosed a DDS-camptothecin which was prepared by binding a camptothecin analog (Compound A) and a carboxy-bearing polysaccharide via gly-gly-phe-glycine. Specifically, it is described that the preservative stabilization of a lyophilized product of DDS-camptothecin is extremely low (See the corresponding European patent 1308171A, paragraphs 0003 to 0005).

Compound A:



Chemical name: (1S,9S)-1-Amino -9-ethyl-5-fluoro-2,3-dihydro-9 γ -hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione

In case that said DDS-camptothecin is compared with the camptothecin analog in Wall et al., the DDS-camptothecin more closely resembles the camptothecin directed to the present invention in respect of containing a carboxy-bearing polysaccharide as a constituent-component. In summary, regarding DDS-camptothecin, there is no motivation to combine Harada et al and Wall et al because the preservative stability with the lyophilized product is extremely low.

In addition, as described in the literature (Shalaev et al., Journal of Pharmaceutical Science 1996, 85 (11), pages 1137-1141) enclosed herewith, the instability of drugs in a liquid preparation is remarkably observed when compared with a solid form such as a lyophilized preparation. However, the aqueous preparation of claim 1, etc. of the present invention shows a highly preservative stability similar to a lyophilized preparation. Accordingly, the unexpected effect of the present invention cannot be deduced from the disclosures in the Harada et al. and Wall et al. references.

In summary, as explained above, the preparation of the present invention shows an excellent preservative stability whether or not it is a lyophilized preparation or an aqueous preparation, and it is submitted that the subject matter claimed in the present application is not taught, disclosed or even suggested in the cited prior art. Thus, allowance of the claims is requested.

As further evidence of the basis for the position taken by the applicant in this case, submitted herewith is a Declaration under 37 CFR 1.132 executed by Mr. Yasuhiro Shindo for consideration herein. The Declaration contains an Attachment (two pages) which comprises data on T-0128 solutions as described in the Harada et al reference. Entry of this document into the file of the present application is respectfully requested.

Table of Paragraph 1.1. of Attachment:

This Table shows the composition of the T-0218 solution disclosed in Paragraph 2.4 (lines 1-11) of the Harada et al reference (prior art). The prior art solution (pH 4) contains a conjugate (T-0218) at a concentration of 100 µg/mL corresponding to 10 mg/100 mL, namely 0.01 w/v% of T-0128. Therefore, the solution of the present invention is distinct from the prior art solution in terms of T-0128 content and pH.

Tables of Paragraphs 1.2.1 to 1.2.3 of Attachment:

Each of the Tables shows the composition of the T-0128 solution disclosed in Paragraph 2.4 (line 11 to the end of the paragraph) of the prior art. Each of the prior art solutions buffered with acetate or phosphate at pH 3, 4, 5, 6 or 7 contains T-0128 at a concentration of 100 µg/mL, namely 0.01 w/v% of T-0128. Therefore, the solution of the present invention is distinct from the above prior art solution in terms of at least one of T-0128 content and pH.

Table of Paragraph 2 of Attachment:

This Table shows the composition of the T-0128 solution for intravenous injection disclosed in Paragraph 2.5 of the prior art. According to this disclosure (line 4), T-0218 was dissolved in saline at 0.5 mg/mL of T-2513 corresponding to 10 mg/mL of T-0128 (namely, 1 w/v% of T-0128). However, it is clear that the prior art solution does not contain any buffer. Therefore, the solution of the present invention buffered at pH 5 to 8 is clearly distinct from the prior art solution.

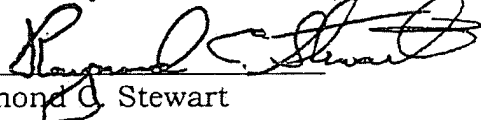
These data provide additional support for the Applicant's position that the pending claims should now be in condition for allowance. Favorable consideration is requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Raymond C. Stewart Reg. No. 21,066 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

Dated: August 8, 2008

Respectfully submitted,

By 
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Attachments: Declaration Under 37 CFR 1.132 and Attachment
Shalaev et al. Journal of Pharm Science 1996 (pp. 1137-1141)